In-vivo assessment of osseous versus non-osseous transmission pathways of vibratory stimuli applied to the bone and the dura in humans

Stump, Reto ; Dobrev, Ivo ; Krayenbühl, Niklaus ; Probst, Rudolf ; Röösli, Christof

Abstract: Background Bone conduction (BC) is an alternative to air conduction (AC) for stimulation of the inner ear. Stimulation for BC can occur directly on the skull bone, on the skin covering the skull bone, or on soft tissue (i.e., eye, dura). All of these stimuli can elicit otoacoustic emissions (OAE). This study aims to compare OAEs generated by different combinations of stimuli in live humans, including direct stimulation of the intracranial contents via the dura, measured intraoperatively. Methods Measurements were performed in five normal-hearing ears of subjects undergoing a neurosurgical intervention with craniotomy in general anesthesia. Distortion product OAEs (DPOAEs) were measured for f2 at 0.7, 1, 2, 3, 4, and 6 kHz with a constant ratio of the primary frequencies (f2/f1) of 1.22. Sound pressure L1 was held constant at 65 dB SPL, while L2 was decreased in 10 dB steps from 70 to 30 dB SPL. A DPOAE was considered significant when its level was 6 dB above the noise floor. Emissions were generated sequentially with different modes of stimulation: 1) pre-operatively in the awake subject by two air-conducted tones (AC-AC); 2) within the same session preoperatively by one air- and one bone-conducted tone on the skin-covered temporal bone as in audiometry (AC-BC); 3) intra-operatively by one air-conducted tone and one bone-vibrator tone applied directly on the dura (AC-DC). A modified bone vibrator (Bonebridge; MED-EL, Innsbruck, Austria) was used for BC stimulation on the dura or skin-covered mastoid. Its equivalent perceived SPL was calibrated preoperatively for each individual by psychoacoustically comparing the level of a BC tone presented to the temporal region to an AC tone at the same frequency. Simultaneously with the DPOAEs, vibrations at the teeth were measured with an accelerometer attached using a custom-made holder. Results It was possible to record DPOAEs for all three stimulation modes. For AC-DC, DPOAEs were not detected above the noise floor below 2 kHz but were detectable at the higher frequencies. The best response was measured at or above 2 kHz with L2 = 60 dB SPL. The acceleration measured at the teeth for stimulation on the dura was lower than that for stimulation on the bone, especially below 3 kHz. Conclusion We demonstrate a proof-of-concept comparison of DPOAEs and teeth acceleration levels elicited by a bone vibrator placed either against the skin-covered temporal bone, as in audiometry, or directly against the dura mater in patients undergoing a craniotomy. It was demonstrated that DPOAEs could be elicited via non-osseous pathways within the skull contents and that the required measurements could be performed intra-operatively.

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Research Paper

In-vivo assessment of osseous versus non-osseous transmission pathways of vibratory stimuli applied to the bone and the dura in humans

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Abstract

Background

Bone conduction (BC) is an alternative to air conduction (AC) for stimulation of the inner ear. Stimulation for BC can occur directly on the skull bone, on the skin covering the skull bone, or on soft tissue (i.e., eye, dura). All of these stimuli can elicit otoacoustic emissions (OAE). This study aims to compare OAEs generated by different combinations of stimuli in live humans, including direct stimulation of the intracranial contents via the dura, measured intraoperatively.

Methods

Measurements were performed in five normal-hearing ears of subjects undergoing a neurosurgical intervention with craniotomy in general anesthesia. Distortion product OAEs (DPOAEs) were measured for f_2 at 0.7, 1, 2, 3, 4, and 6 kHz with a constant ratio of the primary frequencies (f_2/f_1) of 1.22. Sound pressure L_1 was held constant at 65 dB SPL, while L_2 was decreased in 10 dB steps from 70 to 30 dB SPL. A DPOAE was considered significant when its level was ≥6 dB above the noise floor. Emissions were generated sequentially with different modes of stimulation: 1) pre-operatively in the awake subject by two air-conducted tones (AC-AC); 2) within the same session preoperatively by one air- and one bone-conducted tone on the skin-covered temporal bone as in audiometry (AC-BC); 3) intra-operatively by one air-conducted tone and one bone-vibrator tone applied directly on the dura (AC-DC). A modified bone vibrator (Bonebridge; MED-EL, Innsbruck, Austria) was used for BC stimulation on the dura or skin-covered mastoid. Its equivalent perceived SPL was calibrated preoperatively for each individual by psychoacoustically comparing the level of a BC tone presented to the temporal region to an AC tone at the same frequency. Simultaneously with the DPOAEs, vibrations at the teeth were measured with an accelerometer attached using a custom-made holder.

Results

It was possible to record DPOAEs for all three stimulation modes. For AC-DC, DPOAEs were not detected above the noise floor below 2 kHz but were detectable at the higher frequencies. The best response was measured at or above 2 kHz with $L_2 = 60$ dB SPL. The acceleration measured at the teeth for stimulation on the dura was lower than that for stimulation on the bone, especially below 3 kHz.

Conclusion

We demonstrate a proof-of-concept comparison of DPOAEs and teeth acceleration levels elicited by a bone vibrator placed either against the skin-covered temporal bone, as in audiometry, or directly against the dura mater in patients undergoing a craniotomy. It was demonstrated that DPOAEs could be elicited via non-osseous pathways within the skull contents and that the required measurements could be performed intra-operatively.

Keywords: Bone conduction; Dura stimulation; DPOAE; Skull bone vibration; Teeth acceleration; Intraoperative measurements

1 Introduction

Bone conduction (BC) is a means of transmission of energy from a vibratory stimulus applied to the skull that can elicit a hearing sensation. The sensation is similar or equal to that resulting from stimulation by air conduction (AC). Bone conduction testing is used in clinical audiometry to differentiate between a conductive, sensorineural or mixed hearing loss. The investigation of BC has been ongoing for decades, and several different pathways of sound transmission have been described (von Békésy, 1932; Bárány, 1938; Stenfelt and Goode, 2005; Stenfelt, 2015; Tonndorf, 1966). The contribution of each of these pathways to the final sensation of hearing is still a matter of debate. Assuming vibrations are conducted along the bone to the outer ear canal, the middle ear, and the cochlea, the following pathways may be considered: (a) vibration of the cartilage, the bone and the overlying skin of the outer ear canal inducing an air-conducted sound (Stenfelt et al., 2003), (b) inertia of the middle ear ossicles (Stenfelt et al., 2002; von Békésy, 1960), (c) inertia of the cochlear fluids (Stenfelt, 2015), and (d) compression and expansion of the cochlear walls (Tonndorf, 1966; Stenfelt, 2015; von Békésy, 1960). In recent years, several studies have concluded that vibratory stimuli could also be transmitted through non-osseous vibratory pathways, in that vibratory stimuli induce intracranial sound pressures that reach the cochlea through non-osseous connections such as the cochlear or vestibular aqueducts, and perivascular or perineural spaces (Sohmer et al., 2000; Freeman et al., 2000; Ito et al., 2011; Tonndorf and Tabor, 1962). Experiments have shown that placing a vibrator directly on the brain of animals or on different soft-tissue sites without underlying bone in humans can elicit hearing sensations and auditory brainstem responses (ABR), even without inducing significant vibrations of the skull bone (Sohmer et al., 2000; Freeman et al., 2000; Chordekar et al., 2013 (Delete)). Examples of such soft-tissue sites include the fontanelle in infants, the skin over permanent craniotomies, or the eye. Furthermore, vibratory stimuli applied to other parts of the human body, such as the thorax or the neck have also been shown to reach the cochlea (Adelman et al., 2015; Berger et al., 2003; Ravicz and Melcher, 2001).

Ito et al. found similar hearing thresholds for vibratory stimulation on the eye and on the forehead in humans; however, stimulation on the eye induced smaller bone vibrations in the frequency range of 0.5–2 kHz. This finding suggests that low-frequency vibratory stimulation applied to the eye may reach the inner ear via pathways other than skull bone vibrations, indicating different pathway distributions to the inner ear for osseous and non-osseous stimulation sites. A recent study performed on cadaver heads with preservation of intracranial structures and pressures showed that stimulation on the dura and on the mastoid resulted in both bone vibrations and intracranial sound pressures, but with little mutual correlation (Sim et al., 2016). Stimulation of the dura and the mastoid induced comparable intracranial sound pressures above 0.5 kHz; however, promontory vibrations were considerably smaller during dural stimulations. Dural stimulation below 0.5 kHz elicited higher intracranial sound pressures than stimulation on the mastoid.

The influence of intracranial cerebrospinal fluid (CSF) pressure on hearing thresholds has been shown in rats (Freeman et al., 2000). Auditory brainstem response thresholds were temporarily increased after mannitol injection, which reduces the intracranial pressure osmotically. The common clinical observation of a hearing loss primarily in the low frequencies in humans with reduced CSF pressure, for example in dural leakage after spinal anesthesia (Michel and Brusis, 1992) or myelography (Nakaya et al., 2005), supports the assumption of an interaction between CSF and perilymph for hearing. Another possible interaction of CSF and cochlear fluid may result in a low-frequency air-bone gap in pure-tone audiometry that occasionally occurs together with supranormal BC thresholds in patients with semicircular canal dehiscence (SCD) syndrome (Merchant and Rosowski, 2008) and, to a lesser extent, in patients with large vestibular aqueduct (LVA) syndrome (Merchant et al., 2007). Sohmer et al. (2009) suggested that the enlargement of the fluid connections between the cranial cavity and the cochlea results in lower impedance and therefore a more effective sound wave propagation directly from the CSF to the perilymph. However, the mechanism of low-frequency air-bone gap in SCD and LVA has been controversially discussed. Merchant et al. (2007) assumed an increased pressure difference between the scala vestibuli and scala tympani due to decreased impedance in the scala vestibuli by the third window in SCD and LVA, resulting in better BC thresholds. In summary, the actual contribution of such non-osseous pathways to hearing is still controversial.

Laser Doppler vibrometry (LDV) and accelerometry are most commonly used to analyze skull bone vibrations experimentally. Bone vibration is preferentially measured on the skull by pointing an LDV or by coupling an accelerometer directly to bony structures because skin decreases the acceleration response by 16–28 dB, mainly in frequencies above 1 kHz (Ito et al., 2011; Håkansson et al., 1985). Such a direct coupling can be reached using exposed skull bone or an abutment for a bone-anchored hearing aid (BAHA). The dampening effect of the skin has been shown to depend on skin thickness (Mattingly et al. 2015). Teeth as a natural and easily accessible bone-integrated structure are an additional possibility for a direct coupling to facial bones. However, teeth do not directly represent the bone vibrations of the otic capsule (Ito et al., 2011), because skull vibrations may differ depending on location on the skull. Teeth have been identified as an adequate site for BC stimulation in assessment and use of a vibratory BAHA (Stenfelt and Håkansson, 1999).

Additional methods such as threshold measurements or otoacoustic emissions (OAE) are required for investigation of pathways not inducing skull bone vibration. Otoacoustic emissions are objective acoustic responses following cochlear activation and are generated by outer hair cells (Kemp, 1978), and are used routinely for objective evaluation of hearing such as hearing screening in newborns (Probst, 2000). Distortion-product OAE (DPOAE) are commonly elicited in humans by two primary tones (f_1 and f_2) with a frequency ratio (f_2/f_1) of 1.22 and level differences (L_1-L_2) of 0–10 dB (Harris et al., 1989; Hauser and Probst, 1991). They can be elicited by a combination of AC and BC stimuli, providing objective evaluation of the outer hair cells' response (Purcell et al.,1998, 1999; Watanabe et al., 2008; Clavier et al., 2010), and interactions in the cochlea. Purcell et al. (1999) calibrated bone vibrators for

individual subjects objectively comparing DPOAE growth functions elicited with two AC primaries (AC-AC) to the function obtained by one AC and one BC primary (AC-BC). Watanabe et al. (2008) elicited DPOAE by applying a vibratory stimulus to the eye, yielding comparable DPOAE responses as with vibratory stimulation to the forehead. None of these studies measured the skull vibrations induced by BC stimuli to elicit DPOAE.

The goals of this study were 1) to establish a method of eliciting DPOAE with a combined AC stimulus and a stimulus on the dura (DC) and 2) to evaluate how bone vibrations measured at the teeth differ from AC, BC and DC stimulation in humans. We hypothesized that dural stimulation has a comparable sensitivity to mastoid stimulation inducing equivalent DPOAE, and that the induced bony vibrations measured on the teeth would be relatively less at lower than at higher stimulation frequencies. Non-osseous transmission mechanisms may be supposed in the presence of relatively high-amplitude DPOAE together with relatively low-amplitude bone vibrations. Conversely, osseous transmission mechanisms seem more likely in the presence of relatively low DPOAE and high vibration amplitudes.

2 Materials and methods

This study was approved by the Ethics Committee of Canton Zürich (KEK-Nr. 2012-0136) and written informed consent was obtained from all subjects. The study was performed according to the Declaration of Helsinki (2013).

Fig. 1 shows a simplified overview of the hypothesized sound pathways that were activated and tested during the various stimulation scenarios within this work. Air-conducted stimulation (AC-stim.) in the outer ear canal (OE) is transferred through the middle ear (ME) to the inner ear (IE). Vibratory stimulation is applied either to the skin-covered skull bone (BC-stim.) or directly to the dura (DC-stim.) and reaches the IE either through direct communication with the cerebrospinal fluid spaces (CSF) or transmission through the skull bone. Otoacoustic emissions are generated in the IE and measured in the OE (OAE-resp.) indicating the efficacy of transmission for different stimulation sites while teeth acceleration represents the skull bone vibrations (Acc-resp.). Solid lines represent the main pathways and dotted lines illustrate alternative pathways of sound conduction.

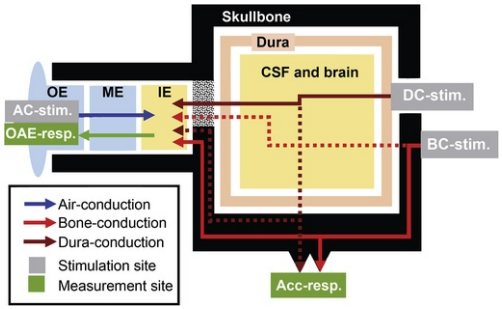

Fig. 1 Model of underlying sound pathways and measurement setup.

alt-text: Fig. 1

2.1 Subjects

Subjects fulfilling the following inclusion criteria were recruited for the study: need to undergo a neurosurgical procedure with a frontal, temporal or parietal craniotomy; age between 18 and 50 years, and the ability to understand and sign the informed consent. The exclusion criteria included bilateral middle or inner ear pathology and a neurosurgical pathology affecting the dura in the area of the planned craniotomy. Subjects also had to present with healthy front teeth to facilitate the acceleration measurements.

Subjects had normal hearing in the test ear, defined as: normal otoscopy; hearing thresholds ≤20 dB HL for AC at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8 kHz, and for BC at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6 kHz; and DPOAE of ≥6 dB above the noise floor (NF) in five out of six measured frequencies. Air conduction thresholds were determined on both sides with a clinical audiometer (Equinox 2.0; Interacoustics, Middelfart, Denmark) and headphones (HDA 280; Sennheiser, Wedemark, Germany) using a conventional bracketing method to obtain responses with a step size of 5 dB. Distortion-product OAE were measured at the frequencies of $f_2 = 1$, 1.5, 2, 3, 4, and 6 kHz using $f_2/f_1 = 1.22$ and $L_1/L_2 = 65/55$ dB SPL. Measurements were done using the Echoport ILO292-II (Otodynamics Ltd, Hatfield, U.K.) together with ILOv6 software (Otodynamics Ltd, Hatfield, U.K.) installed on a Windows-based PC. If the surgical procedure allowed both ears to be considered for intraoperative testing and both fulfilled the inclusion criteria, then the ear with the higher signal-to-noise ratio (SNR) in the DPOAE measurement was chosen.

Bone conduction threshold audiometry was performed for the ear chosen for intraoperative testing using the same audiometer with a bone vibrator placed on the mastoid (Radioear B71; New Eagle, PA, USA). The same conventional bracketing method as described above was used. During this procedure, wide-band masking of 40 dB HL was applied to the contralateral ear using headphones.

2.2 Measurement setup

2.2.1 Signal I/O hardware

In order to allow for the introduction of stimuli through AC, BC and direct dura stimulation, a custom measurement system was used based on two TDT RX6 signal I/O units (Tucker-Davis Technologies, Alachua, FL, USA), one for signal generation and one for signal acquisition (to minimize crosstalk), controlled via PC-based software by TDT (SigGenRP 4.4.8, BioSigRP 100, RX6; Tucker-Davis Technologies, Alachua, FL, USA). Distortion-product OAE in both preoperative AC-AC and AC-BC and intraoperative air- and dura-conducted (AC-DC) measurements were made with the same general parameters (i.e., the frequency and level ratio). The two primary tones f_1 and f_2, with their corresponding levels L_1 and L_2, were generated digitally (SigGenRP 4.4.8, BioSigRP 100, RX6; Tucker-Davis Technologies, Alachua, FL, USA) and routed separately through attenuators (PA5; Tucker-Davis Technologies, Alachua, FL, USA) and a dual-channel amplifier (RMX 850; QSC, Costa Mesa, CA, USA) into the two ER-2 insert earphones (Etymotic Research, Elk Grove Village, IL, USA). The insert earphones were coupled to an ER-10B + microphone system (Etymotic Research, Elk Grove Village, IL, USA) via sound delivery tubes connected to the stainless-steel tubes of the probe. A rubber ear tip sealing the ear canal was attached to the probe. To assure an adequate seal, the sound pressure and spectrum were measured in the ear canal. The assembly was inserted into the ear canal as deeply as possible without any additional fixation to the auricle.

2.2.2 DPOAE recording and processing

The output voltage of the microphone was preamplified with a gain of 20 dB and digitized (RX 6, BioSigRP). Measurement samples of 676-ms duration at each stimulus level and frequency were recorded at a sampling rate of 24,414 Hz resulting in a frequency resolution of 1.49 Hz. Noisy samples (with amplitude variation of more than 10% of the mean of the set) were automatically removed by the system. The samples were averaged in the time domain between 30 and 50 times for $f_2 = 0.75$, 1 and 2 kHz and 10 to 30 times for $f_2 = 3$, 4 and 6 kHz. The amount of averaging was defined manually during the measurements to minimize measurement time while providing sufficient SNR. The time-averaged responses were then automatically transformed to the frequency domain using an 8192-point fast Fourier transform (FFT) algorithm with a Hanning window. The NF was calculated as the mean of the levels of 15 frequency bins (~22 Hz) on each side (total of 30 bins) ±10 frequency bins (~15 Hz) away from the $2f_1$-f_2 frequency, which was the only analyzed DPOAE frequency in this study.

The DPOAE and teeth acceleration data had to fulfill two criteria to be considered present and reliably recorded: first, the SNR had to be ≥ 6 dB; and second, the peak at the $2f_1$-f_2-frequency in the frequency-domain spectrum had to be clearly distinguishable visually from other peaks in the surrounding NF. Data analysis and representation were performed using a custom MATLAB script (MATLAB 2017a MathWorks, MA, USA). The NF in the data is presented as the mean NF.

2.2.3 Stimuli

The frequencies of the primary tones were chosen to yield $2f_1$-f_2 frequencies distant from multiples of 50 Hz as the system occasionally picked up electrical noise in and outside the operating rooms and displayed high peaks (5–10 dB above random NF) at these frequencies. The ratio of the primary tones (f_2/f_1) was kept constant at 1.22. The level of the first primary (L_1) was held constant at 65 dB SPL while the level of f_2 (L_2) was decreased in 10 dB steps from 70 to 30 dB SPL or until no DPOAE could be distinguished from the NF. The $f_2 = 0.75$ kHz condition was measured at the end of each set because measurements at this frequency were time consuming, and DPOAEs were rarely visible. Table 1 provides an overview of the DPOAE stimulus parameters.

Table 1 Overview of DPOAE stimulus parameters and corresponding $2f_1$-f_2 frequencies.

alt-text: Table 1

Primary tone 1		Primary tone 2		Frequency at $2f_1$-f_2 [Hz]
Frequency f_1 [Hz]	Level L_1 [dB SPL]	Frequency f_2 [Hz]	Level L_2 [dB SPL]	
611.02	65	745.15	70, 60, 50, 40, 30	476.89
867.35	65	1058.11	70, 60, 50, 40, 30	676.59
1636.35	65	1994.02	70, 60, 50, 40, 30	1278.68
2470.91	65	3013.08	70, 60, 50, 40, 30	1928.74
3302.50	65	4029.77	70, 60, 50, 40, 30	2575.23
4903.08	65	5982.06	70, 60, 50, 40, 30	3824.10

2.2.4 Bone and dura stimulation

The DPOAEs elicited with one bone or dura conduction (f_2) and one AC (f_1) stimulus were measured with the same setup and parameters as described above. A modified actuator from a Bonebridge® system (MED-EL, Innsbruck, Austria) was used

for bone and dura stimulation. The modification allowed for direct driving of the Bonebridge actuator (bone vibrator) from the amplifier. The bone vibrator from the Bonebridge hearing implant was chosen because it is fully sealed and is designed to be in full contact with bone. A custom holder was coupled to the bone vibrator enabling it to be held in contact with the temporal region via a 5N steel headband for the preoperatively measured AC-BC DPOAE (Fig. 2A).

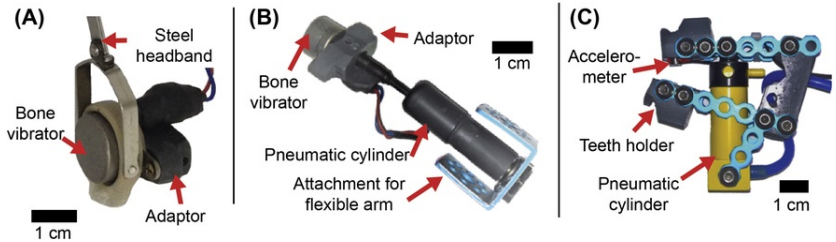

Fig. 2 Customized holders for the bone vibrator and the accelerometer: (A) The vibratory stimulator is attached to the steel headband for the preoperative AC-BC DPOAE measurement. (B) The vibratory stimulator is attached to the pneumatic cylinder via a customized adaptor for the intraoperative AC-DC DPOAE measurement. (C) The accelerometer is firmly inserted into the customized teeth holder that is pressed against the upper incisor teeth.

alt-text: Fig. 2

Preoperatively, the bone vibrator was placed on the temple (“ultrasound window”) directly above the zygomatic arch anterior-superior to the auricle on the same side as the probe inserted into the ear canal. It was kept in place by a steel headband providing a static force of 5 N ~~Newton~~. The temporal region displayed higher reproducibility of the calibrating values in comparison to the mastoid in accordance with the studies by Watanabe et al. (2008) and Ito et al. (2011).

In order to minimize potential risks of damaging the intracranial contents during the AC-DC stimulation scenario, the contact force between the bone vibrator actuator and the dura was minimized. Previous work on dura stimulation in cadaver heads (Sim et al., 2016) have indicated no significant dependence of promontory motion or intracranial pressure on actuator contact force at the dura for frequencies above 1 kHz. Based on that, combined with recommendations from neuro-surgeons and trial tests on cadaver heads, a static contact force of 0.5 N was chosen, 10-fold less than that of a standard steel band. Further, it was not possible to use a steel band intraoperatively due to lack of sterility and available space. To accommodate these constraints, a custom-made pneumatic pusher was used to hold the bone vibrator against the dura during the intraoperative AC-DC DPOAE measurement (Fig. 2B). The pneumatic pusher consisted of a low-friction pneumatic cylinder (glass cylinder with 9-mm diameter graphite piston and 50 mm of travel; Actuator 60657-1, AIRPOT Corporation, CT, USA), which allowed constant and adequate contact force with the dura independent of the relative position between the pusher and the subject's head, thus greatly simplifying intraoperative installation and adjustment of the delicate contact with the dura. A custom adaptor connected the bone vibrator with the piston rod end of the pusher's air cylinder. The pusher assembly was then coupled to a metal rail fixed to the operating table by a Leyla flexible arm (FF273R, FF270, FF282; Aesculap AG, Tuttlingen, Germany), as shown in Fig. 3. The 0.5 N contact force was controlled by varying the pressure (approximately 55 mmHg) in the pneumatic cylinder via a manual blood pressure gauge, including a pump and a manometer, allowing an accuracy of 0.1 N. A custom-made air tank (2 L volume) was added to the pneumatic system to maintain a constant pressure (±10%) in case of a larger displacement of the piston and to compensate for small air leakage (<20 ml/min at 55 mmHg) from the pneumatic cylinder. The air leak was by design and was due to the seal-free construction of the low-friction pneumatic cylinder. The air leak was discharged safely in the protective sleeve away from the patient and, based on trial measurements, did not affect the acoustic or vibration measurements in any detectable manner.

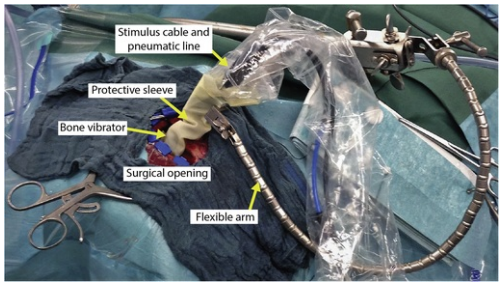

Fig. 3 Intraoperative dura stimulation. The bone vibrator is attached to the pneumatic cylinder via ~~via~~ a customized adaptor and covered with a sterile bag. The assembly is attached to the operating table via ~~via~~ a sterile Leyla flexible fixation arm.

alt-text: Fig. 3

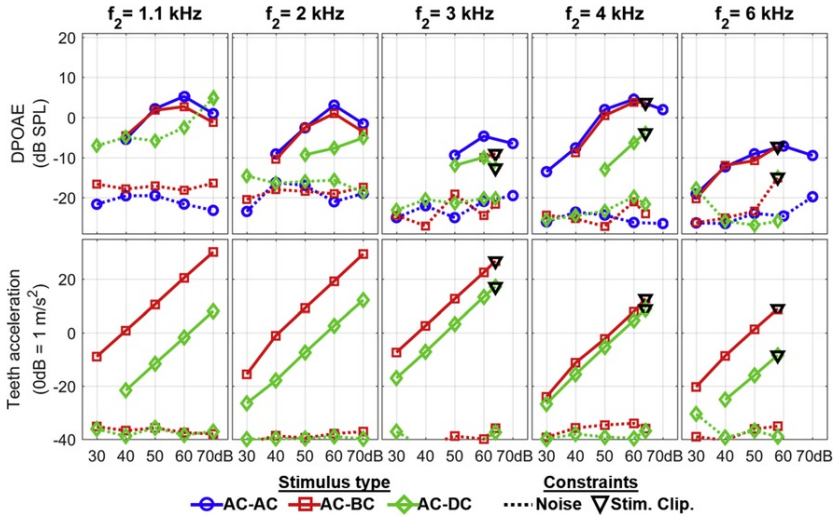

Fig. 4 Results of S1, including DPOAE (top row) and teeth acceleration (bottom row). Note: Solid lines indicate data above the noise floor. Dotted lines indicate noise floor. Colors indicate different stimulation type. Circular markers indicate DPOAE, corresponding to f_3 of the frequency response. Square markers indicate teeth acceleration, corresponding to f_2 of the frequency response. Triangular markers indicate clipped stimulus. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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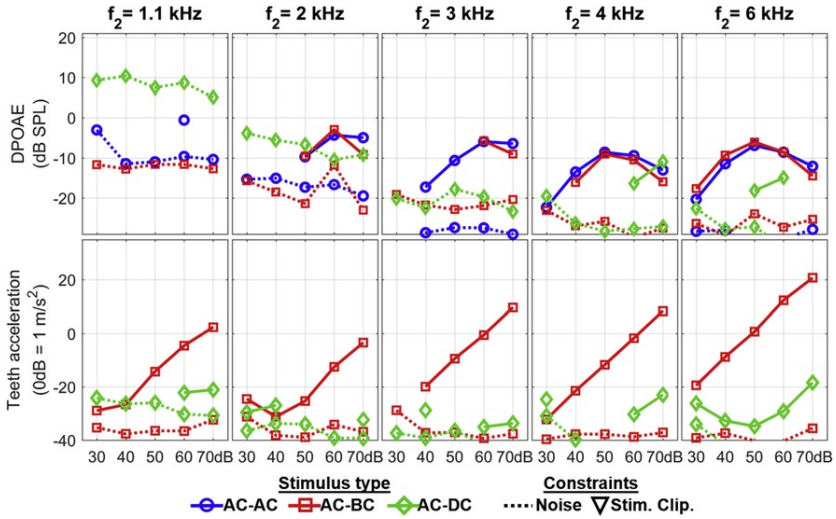

Fig. 5 Results of S3. Note: Solid lines indicate data above the noise floor. Dotted lines indicate noise floor. Colors indicate different stimulation type. Circular markers indicate DPOAE, corresponding to f_3 of the frequency response. Square markers indicate teeth acceleration, corresponding to f_2 of the frequency response. Triangular markers indicate clipped stimulus. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

alt-text: Fig. 5

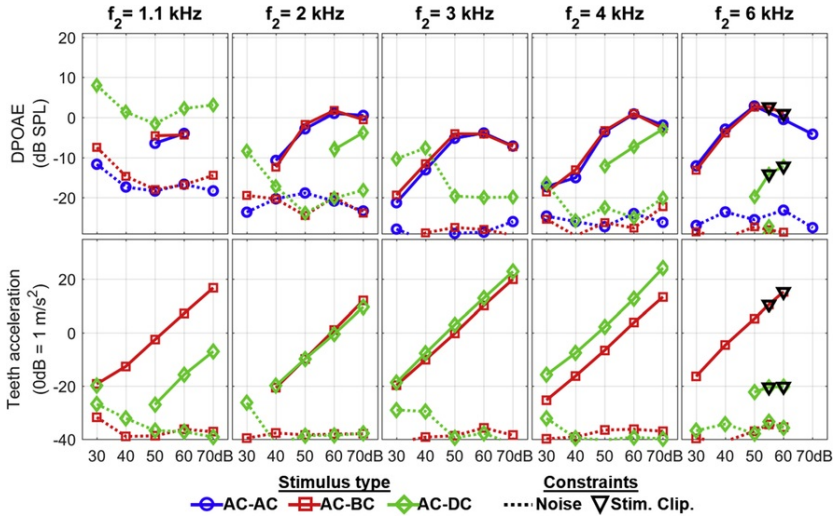

Fig. 6 Results of S4. Note: Solid lines indicate data above the noise floor. Dotted lines indicate noise floor. Colors indicate different stimulation type. Circular markers indicate DPOAE, corresponding to f_3 of the frequency response. Square markers indicate teeth acceleration, corresponding to f_2 of the frequency response. Triangular markers indicate clipped stimulus. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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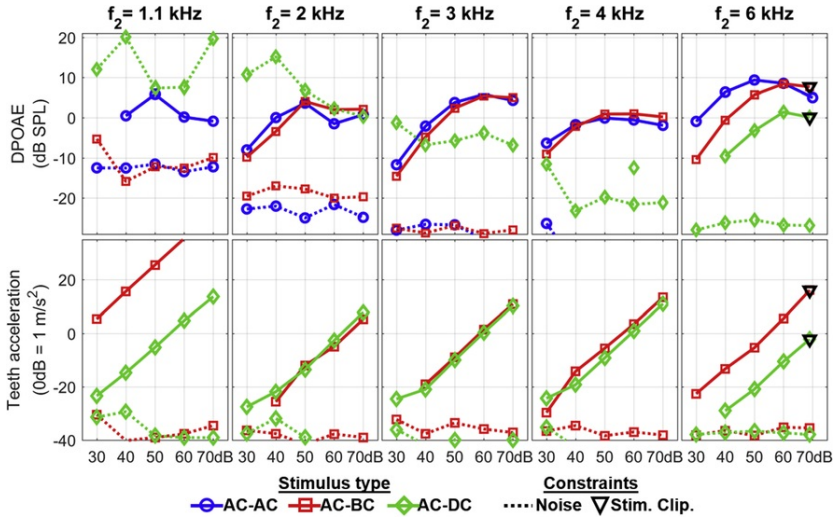

Fig. 7 Results of S5. Note: Solid lines indicate data above the noise floor. Dotted lines indicate noise floor. Colors indicate different stimulation condition. Circular markers indicate DPOAE, corresponding to f_3 of the frequency response. Square markers indicate teeth acceleration, corresponding to f_2 of the frequency response. Triangular markers indicate clipped stimulus. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

alt-text: Fig. 7

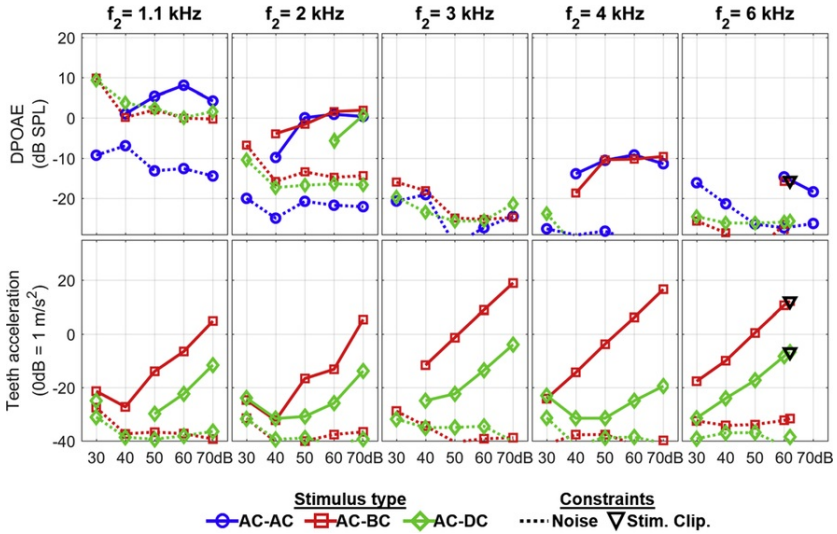

Fig. 8 Results of S6. Note: Solid lines indicate data above the noise floor. Dotted lines indicate noise floor. Colors indicate different stimulation condition. Circular markers indicate DPOAE, corresponding to f_3 of the frequency response. Square markers indicate teeth acceleration, corresponding to f_2 of the frequency response. Triangular markers indicate clipped stimulus. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

alt-text: Fig. 8

2.2.5 Teeth acceleration

Simultaneously with the microphone signal, teeth acceleration during the pre- and intra-operative procedures was measured with an accelerometer (Type 4374; Brüel & Kj æ r, Naerum, Denmark), which was integrated into a custom-made pneumatic holder placed between the patient's front teeth (Fig. 2C). The holder pressed the accelerometer against the upper incisor teeth with a static contact force of 15–20 N using a pressure cylinder connected to an air pump and controlled by a manometer. The signal from the accelerometer passed through a charge amplifier (Type 2635, Brüel & Kj æ r, Naerum, Denmark), where it was amplified and filtered with a 2-Hz high-pass and 10-kHz low-pass filter. The signal was then digitized by the RX6 processor, recorded and displayed in the BioSigRP software after transformation to the frequency domain. Sampling frequency, frequency resolution and number of averages were equal to those used for the ER-10 microphone. Teeth acceleration data reported in this work are based on the magnitude of the accelerometer signal at the f_2 frequency, indicative of the bone conduction component of the BC and DC stimulation.

The teeth acceleration was assumed to represent the skull bone vibrations and corresponding hearing sensation, as shown previously (Ito et al., 2011; Stenfelt and Håkansson, 1995). Teeth acceleration was also chosen as it is readily available in both pre- and intra-operative conditions of the test subjects. The accelerometer in our setup was embedded within an Acrylonitrile butadiene styrene (ABS) plastic piece which in turn was pressed against the teeth by the custom pneumatic holder. The sensitive spatial orientation of the accelerometer was directed towards the upper incisor teeth. This setup was assumed to be similar to previous measurement setups (Ito et al., 2011) as well as to the stimulation setup of a commonly used pre-operative assessment method to test the effectiveness of treatment with a BAHA (Tjellström and Håkansson, 1995). The dependence on the contact force and location was evaluated during preliminary tests by measurements of teeth acceleration on test subjects for continuous BC stimulation at 1 and 4 kHz, sequentially, while the contact force and attachment position were varied. It was observed that for contact forces above 5–10 N, the acceleration readout was nearly independent (1–3 dB variation) of contact location and force. Based on this finding, it was assumed that the coupling between the accelerometer and the teeth was similar in pre- and intra-operative tests, and thus acceleration measurements were comparable. This assumption was necessary as the patient's or surgeon's control over the contact force during the intraoperative measurements was impossible due to the anesthetization and sterile covering.

2.2.6 Calibration of the measurement setup

The acoustic output of the ER-2 earphones was adjusted for each stimulus frequency using a standard ear simulator (Type 4157; Brüel & Kj æ r, Naerum, Denmark) to provide 70 dB SPL. The calibration of the ER-2 earphones was checked before each measurement session and adjusted if necessary. The earphones were tested for linearity using the ear simulator at stimulation voltages equivalent to 80, 70 and 60 dB SPL for each f_1 and f_2. Artefactual distortions of the full system, ER-2 earphones and ER-10 microphone, were tested using ears of cochlear implant users with bilateral deafness. With the exception of one frequency in one of nine tested ears, no significant peaks above the noise floor at the DPOAE frequencies of $2f_1$-f_2 were detected with stimulus levels up to 80 dB SPL, either visually or automatically, using a minimum SNR of 6 dB. We could then conclude that the measured peaks at $2f_1$-f_2 in normal ears were biological in origin rather than artifacts from the system. The ER-10 microphone's linearity was successfully tested in the range from −20 to 100 dB SPL in the anechoic test chamber (Type 4222; Brüel & Kj æ r, Naerum, Denmark).

The bone vibrator's output linearity was checked by coupling it to an artificial mastoid (Type 4930; Brüel & Kj æ r, Naerum, Denmark), which showed sufficient linearity (<1 dB variation for the tested frequency spectrum) for driving voltages at and below 1V and no significant peaks at $2f_1$-f_2. The bone vibrator's output level was calibrated psychoacoustically for each patient individually using the following method. The primary tone f_2 was set at 60 dB SPL for AC at the tympanic membrane, and this stimulus was then alternated between AC and BC presentation. The output of the BC tone was adjusted until it was judged by each subject to be identical in level to the AC tone. All six test frequencies were calibrated in this way using a 1-dB-step resistance attenuator (RA-920; JVCKENWOOD Cooperation, CA, USA). The voltage of the calibrated BC-signal was taken as 60 dB sensation level (SL) for L_2. Since the manufacturer recommended not exceeding a maximum driving voltage of 1 V Volt, the stimulus levels for 60 and 70 dB SL in the higher frequencies were finally either set to the calibrated level or, if exceeding the maximal driving voltage, to 1 V Volt. These instances are referred to as “clipped” in the Results section, and the effective sensation levels in measurements with clipped stimulation levels are presented in Table 2. The non-test ear was masked during this calibrating procedure by a narrow-band masking noise of 60 dB HL with center frequencies corresponding closely to the f_2-frequencies (−18 to +60 Hz) using the audiometer with an insert earphone (E-A-RTONE™ 3A; 3M™, St. Paul, MN, USA).

Table 2 Sensation levels for L_2 in measurements with clipped stimulation levels.

alt-text: Table 2

Target SL [dB]	30	40	50	60	70
Subject – f_2					
S1 – 3 kHz	30	40	50	60	66
S1 – 4 kHz	30	40	50	60	66
S1 – 6 kHz	30	40	50	58	58
S4 – 6 kHz	30	40	50	55	60
S5 – 6 kHz	30	40	50	60	69
S6 – 6 kHz	30	40	50	60	62

The force of the pneumatic cylinder that held and pressed the bone vibrator against the dura intraoperatively was calibrated with a dial tension gauge gram force meter (1 g F gF resolution and 150 g F gF range; ATG 150-2, Zhejiang Holdwell Group Limited, China).

2.3 Measurement procedures

2.3.1 Preoperative DPOAE measurements (AC-AC and AC-BC)

First, AC-AC DPOAE were elicited with the primary tones routed separately to the ER-2 earphones and mixed acoustically in the outer ear canal, as shown in Fig. 1. Next, the subject participated in the calibration of the bone vibrator for each f_2 individually as described above. The DPOAEs were then measured presenting f_1 via AC and f_2 via BC. The L_1 was again held constant at 65 dB SPL while L_2 was changed from 70 (or clipped stimulation level) to 30 dB SL in 10-dB steps. Acceleration at the frequency of f_2 was measured simultaneously. Only subjects with AC-BC DPOAE of ≥6 dB above the NF for at least one stimulation level at $f_2 = 2$, 3, 4 and 6 kHz were included for the intraoperative measurements. As intraoperative measurements of valid AC-BC DPOAE at $f_2 = 0.75$ and 1 kHz were highly unlikely due to the high NF in the operating room (OR), S3, S5, and S6 were included without having preoperatively valid AC-BC DPOAE at those frequencies. Subject S6 did not have valid AC-BC DPOAE at 3 kHz in the preoperative tests. Since AC-BC DPOAE at 2 and 4 kHz were well above the NF, it was decided to proceed with intraoperative measurements. Preoperative measurements were performed in a sound-treated room in a single session on the day before surgery. The total measurement time was approximately 75 min for the preoperative tests, including calibration, AC-AC, and AC-BC.

2.3.2 Intraoperative DPOAE measurement (AC-DC)

Intraoperatively, only DPOAE evoked by a combination of AC and dural-vibration stimuli (AC-DC DPOAE) were measured using principally the same set-up and parameters as used for AC-BC. The accelerometer device was placed between the patient's front teeth after anesthesia and endotracheal intubation. The same ear probe as used for the preoperative DPOAE measurements containing the insert earphone for f_1 was placed in the external ear canal, again without any additional fixation to the auricle. The cables were fixed to the operating table to avoid any tension on the probe. Once the craniotomy was completed, the vibrator was brought into contact with the dura under sterile conditions (Surgi-Boot™ Transducer Cover, Ref 610–797; Civco, IA, USA), and a static pressure of 0.5 N was applied (Fig. 3). The surgeon visually checked that the bone vibrator did not touch the surrounding skull bone. The measurement was then performed with the same stimulation frequencies and levels as in the AC-BC DPOAE measurement preoperatively. The maximum duration of the intra-operative measurement was 15 min. Surgical activities were ceased during this time, and noise in the OR was reduced as much as possible by restricting verbal

communication and muting monitoring devices. All measurements were performed by the same investigators.

3 Results

3.1 Subjects

Intraoperative measurements were obtained from seven subjects, but two of these were unsuccessful. In S2, an unexplained, excessively high NF was encountered and in S7, a system malfunction occurred during the intraoperative measurements. In four out of five successful measurements, the ear contralateral to the craniotomy was measured either due to better responses preoperatively, space availability, or the surgeon's preference. The ear on the same side as the craniotomy was tested in S5. Table 3 presents an overview of the five subjects finally included in the results.

Table 3 Characteristics of the individual subjects included for further analysis.

alt-text: Table 3

Subject	Age	Sex	Diagnosis	Site of Craniotomy	Tested ear
S1	35	M	Astrocytoma Grade II	Frontal, right	Left
S3	22	M	Cavernoma	Parietal, right	Left
S4	38	M	Vestibular schwannoma	Temporal, right	Left
S5	36	F	Electrode implantation	Parietal, right	Right
S6	38	M	Vestibular schwannoma	Temporal, right	Left

3.2 DPOAE measurements

No reliable DPOAEs could be obtained for $f_2 = 0.75$ kHz, either for preoperative AC-BC measurements or for intraoperative AC-DC measurements due to the high NF. Therefore, the results for $f_2 = 0.75$ kHz were not further analyzed.

Clipping of maximal driving voltage provided to the bone vibrator at 1 V ~~Volt~~ was necessary in S1, S4, S5 and S6 for $f_2 = 6$ kHz at $L_2 = 70$ dB SL, in S1 and S4 for $f_2 = 6$ kHz at $L_2 = 60$ dB SL, and additionally in S1 for $f_2 = 3$ and 4 kHz at $L_2 = 70$ dB SL. Table 2 presents the effective sensation levels used in the measurements with clipped BC and DC stimulation levels. Data points with clipped levels are marked with triangles in Figs. 4–8.

In preoperative measurements, DPOAEs evoked by combined stimulation of AC (f_1) and the vibrator (f_2) positioned at the temple region over the skin were similar to DPOAEs evoked by two AC-delivered primaries for all frequencies, indicating well-calibrated stimulation levels for the BC stimulator (red squares and blue circles in Figs. 4–8). No further analysis of AC-AC versus AC-BC measurements was performed.

Intraoperative measurements were limited by the relatively high background noise in the OR environment, particularly at lower frequencies. No intra-operative DPOAEs were obtained at $f_2 = 1$ kHz. The intraoperative NF at $f_2 = 2$ and 3 kHz was more variable than that at $f_2 = 4$ and 6 kHz. All five subjects showed AC-DC DPOAE for at least one stimulation frequency above 1 kHz. Individual measurements for AC-DC DPOAEs were highly variable. In general, AC-DC DPOAEs tended to show similarly shaped growth curves as AC-BC DPOAE measurements, though with clearly reduced DPOAE levels. Because of the extensive variability across subjects, the characteristics of the recordings from the participants are presented individually (Figs. 4–8). Only data with an SNR of ≥6 dB and considered to be a biological response are displayed.

3.3 Acceleration measurements

Vibrations measured on the teeth for both preoperative BC and intraoperative DC stimulation were present in four subjects. Subject S3 exhibited intraoperative acceleration levels above the NF only for higher frequencies and at stimulation levels of $L_2 = 60$ and 70 dB SL. Acceleration levels generally showed a linear growth pattern with increasing stimulation levels for both BC and DC stimulations. Acceleration levels varied between subjects with DC-stimulation resulting in smaller, equal or even higher (S4) acceleration levels compared to BC-stimulation.

3.4 Individual subject data

Fig. 4 displays data for S1, where preoperative AC-BC DPOAEs (red circles) were present at all frequencies with saturation present at $L_2 = 60$ dB SL. Intraoperative AC-DC DPOAEs (green circles) could be measured at $f_2 = 2$–6 kHz. The intraoperative NF for $f_2 = 1.1$ kHz was greater compared to preoperative testing while similar pre- and intraoperative NF were noted for $f_2 = 2$–6 kHz AC-DC DPOAE measurements, which were 0–15 dB less than

comparable AC-BC DPOAE levels. The lower panels represent corresponding acceleration measurements on the front teeth. The acceleration levels at the f_2-frequency are also displayed in Fig. 4. Teeth acceleration levels exhibited linear growth at all frequencies for BC (red squares) and DC (green squares). Better transmission of BC stimuli was found for lower frequencies. Best transmission for DC was noted at $f_2 = 3$ kHz with progressively smaller vibrations at lower and higher frequencies resulting in similar acceleration levels for BC and DC at $f_2 = 4$ kHz. For $f_2 = 2$ kHz, the difference in acceleration of BC and DC was 20 dB. The DPOAE for combined AC-BC and AC-DC stimulation also differed, as indicated on the x-axis. For stimulation at $f_2 = 4$ kHz, BC and DC resulted in equal acceleration levels but not in the corresponding growth functions of DPOAE levels.

Fig. 5 displays data for S3, where preoperative AC-BC DPOAE (red circles) at $f_2 = 1.1$ kHz were uncertain with small DPOAE levels. Saturation of DPOAE levels for $f_2 = 2$ and 3 kHz was present at $L_2 = 60$ dB SL and for $f_2 = 4$ and 6 kHz at $L_2 = 50$ SL. Intraoperative AC-DC DPOAE measurements (green circles) showed high NF at $f_2 = 1$ and 2 kHz, resulting in no detectable DPOAE. For $f_2 = 3$–6 kHz, the NF was similar to the preoperative measurements. The AC-DC DPOAEs could be recorded only for $f_2 = 4$ kHz/$L_2 = 60$ and 70 dB SL, and at $f_2 = 6$ kHz/$L_2 = 50$, 60 and 70 dB SL. A steep increase was noted for stimulation levels of $L_2 = 60$ dB–70 dB SL. Corresponding (similar level) AC-BC and AC-DC DPOAE levels are shifted by roughly 20 dB to the right for display purposes.

Teeth acceleration measurements were valid and linear responses obtained at all frequencies for BC (red squares) stimulation, with highest levels at 6 kHz. The DC (green squares) stimulation did not induce unequivocal vibrations at most levels and frequencies. Teeth vibrations may have been present at 4 kHz/70 dB SL and 6 kHz/60 and 70 dB SL.

Fig. 6 displays data for S4, where preoperative DPOAE measurements for the AC-BC stimulus type (red circles) indicated no valid data at $f_2 = 1.1$ kHz. For the rest of the frequencies, the DPOAE levels showed a consistent trend at all frequencies with saturation at L_2 of 50 or 60 dB SL. The intra-operative AC-DC DPOAEs (green circles) showed high NF at $f_2 = 1$ and 3 kHz, masking any possible DPOAE, while for $f_2 = 2$, 4, 6 kHz, the NFs were similar to preoperative measurements, and data were available for $L_2 \geq 60$ dB. The AC-DC DPOAE levels were approximately 10 dB smaller than for AC-BC, limiting definitive measurements to $L_2 \geq 60$ dB SL at 2 kHz and $L_2 \geq 50$ dB SL at 4 kHz. Markedly smaller DPOAE levels were present for $f_2 = 6$ kHz.

Teeth acceleration showed valid data and a linear response at all frequencies for the BC (red squares) condition. At 2, 3 and 4 kHz, similar levels of teeth vibrations were induced by DC (green squares) as by BC. Clearly smaller vibration levels were measured for DC at 1.1 kHz and no clear vibrations were present at 6 kHz. Despite similar acceleration levels at $f_2 = 2$ kHz for BC and DC, the corresponding AC-DC DPOAE levels were markedly lower than the AC-BC DPOAE levels.

Fig. 7 displays data for S5, where preoperative DPOAE measurements for AC-BC stimulus type (red circles) indicated no response present at $f_2 = 1.1$ kHz. Levels at $f_2 = 2$–6 kHz showed saturation at $L_2 = 50$ or 60 dB SL.

The intra-operative AC-DC DPOAE (green circles) showed high NF at $f_2 = 1.1$–3 kHz. The AC-DC DPOAEs could be obtained only at $f_2 = 6$ kHz and were 10 dB below the AC-BC DPOAEs. The lower panels represent acceleration measurements on the front teeth.

Teeth acceleration showed valid data and a linear response at all frequencies for the BC (red squares) condition. The same amount of teeth vibrations was induced by BC (red) and DC (green) at 2, 3, and 4 kHz, while DC-induced smaller vibrations were present at 1.1 and 6 kHz. At $f_2 = 6$ kHz, DC-induced acceleration levels were 15 dB and AC-DC DPOAEs were 10 dB below the corresponding BC-induced acceleration levels and AC-BC DPOAEs, respectively. At $f_2 = 4$ kHz, AC-DC DPOAEs were only present for $L_2 = 60$ dB SL despite similar acceleration levels for BC and DC.

Fig. 8 displays data for S6, where preoperative DPOAE measurements for the AC-BC stimuli (red circles) resulted in data only at $f_2 = 2$, 4 kHz and 6 kHz with saturation at $L_2 = 50$ or 60 dB SL. The intra-operative AC-DC DPOAE (green circles) data indicated high NF at $f_2 = 1$ kHz. No DPOAEs were present except at 2 kHz/$L_2 = 60$ and 70 dB SL.

Teeth acceleration showed valid data and linear response at all frequencies for the BC (red squares) condition, except for 2 kHz, where data plateaued between $L_2 = 50$ and 60 dB SL. The DC-induced vibrations (green squares) were markedly smaller compared to corresponding BC-vibrations, potentially explaining the overall poor quality of the AC-DC DPOAE data at other frequencies.

4 Discussion

4.1 Experiment complexity and data variability

This work presents experimental evidence of stimulation of the outer hair cells induced by direct vibratory stimulation of the human dura, as indicated by DPOAE measurements. The two stimulation tones (f_1 and f_2) were presented by air conduction and via direct vibratory stimulation of the dura exposed during neurosurgical procedures. Distortion-product OAEs could be recorded, but with considerable variability across the five subjects, as seen by the overview of the averaged data in Fig. 9. As shown in the top and middle panels, the recordable DPOAEs were present primarily in the frequency range above 2 kHz and were at levels 5–15 dB lower than DPOAE evoked by a combination of AC and BC stimuli, measured preoperatively under standard audiometric conditions. The averaged data points were plotted in Fig. 9 only when data were available for at least three subjects.

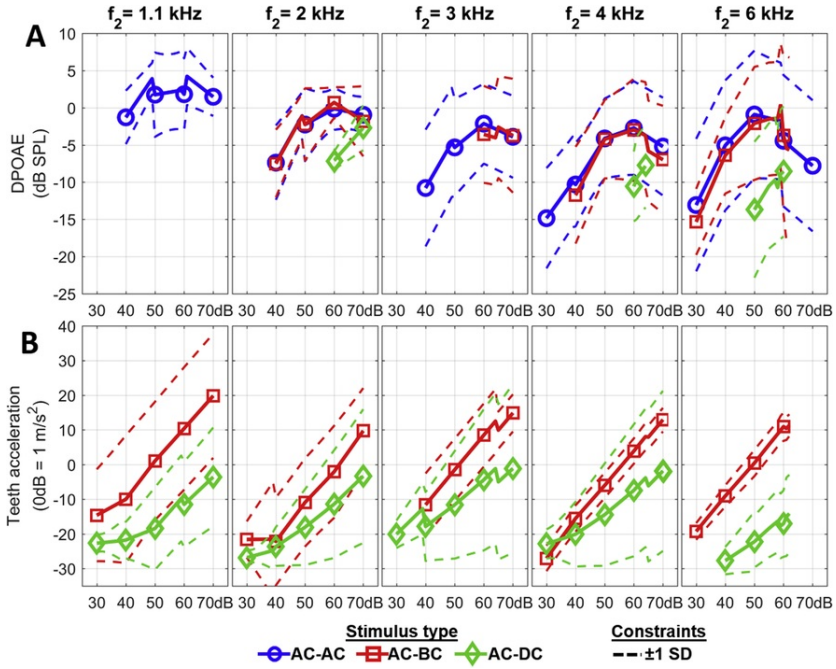

Fig. 9 Comparison of averaged results across patients, including mean and one standard deviation confidence interval of: A) DPOAE from AC-AC and AC-BC stimulation; B) DPOAE from AC-BC and AC-DC stimulation; and C) Teeth acceleration, from AC-BC and AC-DC stimulation. Solid lines indicate mean data. Dashed lines indicate a confidence interval of 1 standard deviation. Colors indicate different stimulation conditions. Circular markers indicate DPOAE, corresponding to f_3 of the frequency response. Square markers indicate teeth acceleration, corresponding to f_2 of the frequency response. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

alt-text: Fig. 9

The measurements of the preoperative AC-BC DPOAE and the intraoperative AC-DC DPOAE were combined with an acceleration measurement on the front teeth for the recording of bone vibrations induced by the vibratory stimulus, indicating the vibrational energy propagating through bony structures, as opposed to soft tissue or the CSF. Intraoperative data of teeth acceleration, recorded in four of the five subjects, indicated high variability in both absolute levels as well as in the ratio between DC and BC stimulations, as indicated by the large (20–40 dB) confidence intervals displayed in Fig. 9 (bottom).

The measurements of DPOAEs evoked by a combination of AC and direct vibratory stimulation of the dura were complex, technically demanding, and intricate. We modified a commercially available implantable bone vibrator (MED-EL Bonebridge®) for direct dural stimulation during surgery. The device proved to be an effective and reliable tool when used as a bone vibrator in a standard audiometric environment. Distortion products evoked by a combination of AC stimulation through an insert earphone and the Bonebridge device as an audiometric bone vibrator on the temple region were recorded reliably, with SNRs in the range of 10–40 dB, which is in agreement with results reported in the literature (Purcell et al., 1999; Watanabe et al., 2008). The psychoacoustic calibration procedure between the AC and BC stimuli made it possible to generate L_2 that resulted in similar DPOAE levels at all stimulation levels and frequencies, as seen in Fig. 9A.

The AC-DC measurements with stimulation of the open dura during surgery in the OR presented multiple challenges for DPOAE recordings. The recording time was restricted to 15 min with the intention of avoiding undue prolongation of the patient's time during surgery. Direct stimulation of the dura was considered safe for the following reasons. First, the Bonebridge device is routinely implanted with more or less direct contact to the dura without any known disadvantages (Vyskocil et al., 2017). Second, it is known from cadaver head studies that intracranial pressure for stimulation on the dura is comparable to levels of stimulation on the skull bone (Sim et al., 2016). We restricted the stimulation level equivalent to no more than 70 dB SL. Finally, the pressure on the dura was kept at a low level of 0.5 N and direct contact to brain structures was avoided.

The random noise floor in the OR was relatively high and not readily controllable, particularly in the low-frequency range up to 2 kHz. There were additional noise sources at specific frequencies (e.g., 50 Hz), the influence of which was reduced through adequate selection of the primary tones. Additional variability may have resulted from different placements of the transducer during dural stimulation, which also necessitated individual arrangements of the instrumentation set-ups while respecting sterile draping and neurophysiological monitoring devices. Moreover, the distances between the stimulation site and the inner ear or the front teeth were not constant, in contrast to the AC-BC

measurements before surgery. Distortion product OAEs to AC-DC were measured ipsilateral to the craniotomy only in S5, meaning that any distance-related dampening was supposedly smaller than in the other subjects. However, the DPOAE level difference between AC-BC and AC-DC stimulation at $f_2 = 6$ kHz was similar to differences in the other subjects. Correspondingly, Watanabe et al. (2008) found small DPOAE level differences for stimulation at the ipsilateral versus contralateral eye, but large DPOAE level differences for stimulation at the ipsilateral versus contralateral mastoid. This may indicate that stimulation on dura or the eye is less susceptible to laterality of stimulation. However, this may need further experimental verification.

Because of all these limitations and restrictions, we presented the individual results of the five subjects. These demonstrate proof-of-concept findings regarding the underlying physiology of intracranial sound transmission in humans. Predictably, results were highly variable, and we were not able to fit them to a consistent pattern. This is clearly evident by comparing the data in Fig. 9 with the individual displays in Figs. 4–8.

Dural stimulation did not evoke larger DPOAE levels than did pre-operative BC stimulation. The AC-DC DPOAEs were 5–15 dB smaller than preoperatively acquired AC-BC DPOAEs, as seen in Fig. 9B. The growth of AC-DC DPOAE levels with increasing stimulation levels seemed to be similar to that of AC-BC DPOAEs, but saturation was often not reached because the stimulus level was limited.

We conclude that dura conduction is less efficient as a stimulus for activation of the outer hair cells than bone vibration at frequencies ≥2 kHz. In other words, DC requires higher stimulation levels to induce the same level of cochlear activation as BC, at least in the higher frequency range. The results of Watanabe et al. (2008) showed similar level differences for DPOAE when the stimulation was on the temporal window compared to the soft tissue of the eye. Moreover, experimental findings on cadaver heads have shown that promontory acceleration is lower for stimulation to the dura compared to stimulation on the mastoid; whereas, intracranial pressure is comparable for frequencies >500 Hz (Sim et al., 2016). For stimulation on other soft tissue sites such as the eye or the neck, the ratio of promontory motion to intracranial pressure was found to be comparable (Röösli et al., 2016). These findings indicate different stimulations of the skull bone and intracranial contents from vibratory stimulation at different soft tissue sites.

One presumed reason for the smaller DPOAE levels with DC stimulation is the reduced coupling force of the dural vibrator. Due to safety reasons, we limited the coupling force on the dura to 0.5 N and monitored it during the measurement. In a study with dural stimulation in cadaver heads, an increased coupling force resulted in only moderate gain (2–5 dB) of intracranial sound pressure without inducing a consistent increase in promontory vibration (Nakaya et al., 2005). A coupling force of at least 4 N is generally recommended for audiometric BC measurements to receive clinically reliable results (Ito et al., 2011). We decided to use standard audiometric coupling forces of 5 N for our preoperative BC measurements and not to reduce the pressure on the temple to 0.5 N, mainly because of the well-known dampening effect of intact skin. Previous studies have presented contradictory results concerning the frequency-dependent effects of static coupling force on the output of a BC stimulator (Ito et al., 2011; Adelman and Sohmer, 2013; Toll et al., 2011). Adelman and Sohmer (2013) showed a significantly better perceptual response threshold at 2 kHz with a coupling force of 5 N compared to 1 N for stimulation on soft tissue sites on skin without underlying bone. No systematic assessment has been performed for determining the effects of coupling force on direct stimulation of intracranial structures or the eye. In previous studies, the bone vibrator was either held manually by the participants or the investigators without objective control of the applied pressure [Sohmer et al., 2000; Watanabe et al., 2008], or the measurements with the vibrator on the eye were performed with a single coupling force of 2 N (Ito et al., 2011). Freeman et al. (2000) reduced the pressure from 1.14 N, which was in the initial experimental design, to 0.26 N in experiments with stimulation on the brain in rats and guinea pigs because the higher pressure deformed the brain. The different coupling forces between stimulation on the dura and on the temple and mastoid may have contributed to DPOAE differences. This constitutes an obvious limitation of this study.

Because of its size, the clinical implantation of a Bonebridge can result in contact of the device with the dura and/or the sigmoid sinus. Vyskocil et al. (2017) reported such a contact in 19 of 38 patients receiving a Bonebridge. Interestingly, the functional hearing gain was not significantly higher in patients with soft tissue contact compared to those with a classical “bone-only” application of the device. Sim et al. (2016) compared intracranial sound pressure level and promontory vibration in cadaver heads for dura versus mastoid stimulation. They found a comparable ratio of intracranial sound pressure and promontory motion for all stimulation modes with frequencies of <2 kHz. A high noise level made it impossible to draw conclusions in the frequency range <2 kHz. Our study had limitations in measurement capabilities for the low frequencies.

Technical factors can have a detrimental influence on the reliability of DPOAE measurements, possibly even more so when different means of stimulation are used and become combined. We tried to control for these factors as much as possible. First, an occlusion effect by the insertion of the probe into the outer ear canal probably did not have an effect on our results because the probe provided only one stimulus, and we were not able to record DPOAEs at lower frequencies. The occlusion effect is known to inflate BC hearing threshold levels only below 2 kHz (Stenfelt et al., 2003). In addition, we inserted the probe as deeply as possible, as suggested by Dean and Martin (2000).

Secondly, our set-up did not include a level adjustment of the AC stimulus to individual variations in the ear-canal volume, but we do not think that this lack had a critical influence on the variability of our results. Only adult subjects were included, and Whitehead et al. found that a reduction in the variability of DPOAE amplitudes was not achieved by performing an in-the-ear adjustment of the stimulus SPL for individual resonance characteristics (Whitehead et al., 1995).

Thirdly, changes in intracranial pressure can influence hearing threshold levels and DPOAEs. Intracranial pressure may increase when measuring in a prone rather than a sitting position (Voss et al., 2010), as was the case when AC-DC measurements were compared to AC-BC measurements. However, the phase of DPOAE is generally more affected than magnitude with positional changes. By contrast, a craniotomy may lower intracranial pressure. Walsted et al.

(1994) reported a temporary hearing loss after craniotomy, but only in patients with a concomitant opening of the dura resulting in a reduction of the intracranial pressure. We took care to perform our measurements without an intentional opening of the dura after removal of the skull bone only. Therefore, we are assuming only minor changes of intracranial pressure and DPOAE levels as a result. The anesthesia most likely did not affect the DPOAEs. Telischi et al. (1995) did not find any significant impact of general anesthesia on DPOAE levels, which is in accordance with the findings by Ropposch et al. (2014), who did not show a significant DPOAE level difference between patients anesthetized with sevoflurane and those with propofol for f_2 between 2 and 8 kHz.

Fourthly, it was not possible to match the actual loudness of dura stimulation to the AC or BC stimulus. Stimulus levels applied to the dura may have differed to an unknown extent.

Lastly, we took every precaution to avoid technically related artifacts that would create distortions of our measuring system. Such distortion may occur and may be difficult to distinguish from biological responses, particularly at higher stimulation levels (Hauser et al., 1991). Our equipment was checked before each set of measurements for nonlinear distortions, and we applied strict definitions and conditions concerning when to consider data points to be valid DPOAE recordings.

The levels of skull vibrations measured on the front teeth and induced by either BC or DC stimulation impressively illustrate the variability of our results. While acceleration levels during DC stimulation were recorded clearly in the frequency range of 1–6 kHz for S1 and S5, they were found only in a restricted frequency range or with small amplitudes for S4 and S6, and not at all for S3. If a vibrator on the dura without contact to the bone applies f_2 stimulation, then the presence of DPOAE without vibrations of the skull at f_2 will demonstrate an efficient and nearly exclusive propagation of the dural stimulus to the inner ear without induction of bone vibrations. Only the results of S3 may support such a pattern, but DPOAEs were small in this subject in the intraoperative condition. By contrast, acceleration levels at f_2 were sometimes even larger for dural than for audiometric bone vibrations, indicating an efficient propagation of dural and soft tissue vibrations to the surrounding bony shell of the skull for stimulation between 30 and 70 dB SL. Cochlear stimulation may be through BC rather than through soft tissue connections in these cases. Acceleration levels were similar for BC and DC in the frequency range of 2–4 kHz in S4 and S5. Levels of DC were clearly lower than BC in S1 and S6, with the exception of 4 kHz in S1. One reason for this finding may be the fact that responses could be recorded only for frequencies ≥2 kHz. Ito et al. (2011) demonstrated that vibratory stimulation of the eye provoked increasing teeth vibrations with increasing frequencies, and that teeth vibrations reached levels similar to standard audiometric BC stimulation levels at about 2 kHz. Vibration levels also became more variable at higher frequencies, just as in our subjects.

It is remarkable that in one subject (S4), DC stimulation could induce larger acceleration levels for measurements on the teeth than BC stimulation on the temporal region, using the same vibratory device and identical stimulus parameters. We can only speculate that perhaps different resonances due to individual tissue characteristics, subject-specific locations of the dural stimulation, or individually variant intracochlear interactions of the dural and AC-stimulus (Mcleod and Culling, 2017) may have contributed to these variations. It is also important to realize that acceleration at the teeth does not faithfully represent vibrations of the otic capsule, as was demonstrated by Ito et al. (2011) and Sim et al. (2016) for vibrations of the mastoid bone and the promontory. Additionally, acceleration measurements at the teeth for both dural or BC stimulation showed high individual variability in the present study.

5 Conclusion

The present study has demonstrated that direct vibratory stimulation of the dura induces cochlear stimulation, which is lower in amplitude when compared with the same frequency of stimulation to the temporal bone. It must be assumed that a substantial amount of the transmission of the dural vibratory energy to the inner ear for frequencies ≥2 kHz is through osseous rather than non-osseous pathways because high acceleration levels of the teeth were present. Because dura-conducted cochlear stimulation was possible despite the difficult measurement environment in the OR and the factors discussed previously, this is considered a proof-of-concept study that demands future research be conducted to investigate the characteristics of DPOAE with dural stimulation, in particular for lower frequency and threshold level stimuli.

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Uncited References

World Medical Association, 2013.

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Highlights

- Direct vibratory stimulation on the dura activates the outer hair cells, indicated by DPOAE.
- For frequencies ≥ 2 kHz, stimulation on dura induces a comparable DPOAE amplitude as for stimulation on the skin-covered temple at 70 dB, but lower amplitudes at lower levels.
- Direct stimulation on the dura induces skull vibrations, measurable at the teeth.

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